

Infliximab for Maintenance of Glucocorticosteroid-Induced Remission of Giant Cell Arteritis

A Randomized Trial

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Background: Tumor necrosis factor- α is present in arteries in giant cell arteritis.

Objective: To evaluate the efficacy of infliximab, an anti-tumor necrosis factor- α agent, in giant cell arteritis.

Design: Randomized, controlled trial.

Setting: 22 sites in the United States, the United Kingdom, Belgium, Italy, and Spain.

Patients: 44 patients with newly diagnosed giant cell arteritis that was in glucocorticosteroid-induced remission.

Intervention: Participants were randomly assigned in a 2:1 ratio to receive infliximab (5 mg/kg of body weight) or placebo. Sixteen patients were assigned to glucocorticosteroid plus placebo, and 28 patients to glucocorticosteroid plus infliximab.

Measurements: End points were measured through week 22, when an interim analysis resulted in early stopping of the planned 54-week trial. Primary end points were the number of patients who remained free of relapse through week 22 and adverse events. Secondary end points were time to first relapse, biomarkers, cumulative glucocorticosteroid dose, and the number of patients who remained relapse-free while the glucocorticosteroid dosage was tapered to 10 mg/d.

Results: Infliximab therapy did not increase the proportion of patients without relapse at week 22 compared with placebo (43% vs. 50%, respectively; difference, -7 percentage points [95% CI, -38 to 23 percentage points; $P = 0.65$], nor did it increase the proportion of patients whose glucocorticosteroid dosages were tapered to 10 mg/d without relapse (61% vs. 75%, respectively; difference, -14 percentage points [CI, -42 to 14 percentage points]; $P = 0.31$). The incidence of infection was 71% with infliximab and 56% with placebo (difference, 15 percentage points [CI, -14 to 45 percentage points]).

Limitations: The sample was too small to rule out modest effects of infliximab and included only patients with a new diagnosis. Only one dose of infliximab was evaluated, and the study was terminated early.

Conclusions: This trial is too small to draw definitive conclusions, but it provides evidence that using infliximab as maintenance therapy in patients in glucocorticoid-induced remission of newly diagnosed giant cell arteritis is of no benefit and may be harmful. If infliximab has benefit, it is unlikely to be great.

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*For a list of the members of the Infliximab-GCA Study Group, see the Appendix (available at www.annals.org).

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In northern Europe and North America, the estimated annual incidence of giant cell arteritis is 19 to 32 cases per 100 000 persons older than 50 years of age. In Mediterranean countries, the annual incidence appears to be lower: 6 to 10 cases per 100 000 persons (1-5). Treatment with glucocorticosteroids dramatically alters the symptoms and course of giant cell arteritis, reducing the likelihood that the patient will develop blindness (6, 7). However, relapses usually occur when glucocorticosteroid dosages are tapered, resulting in frequent re-treatment and glucocorticosteroid dependence and toxicity (8-10). Approximately 80% of patients with giant cell arteritis will eventually experience at least 1 adverse event attributable to glucocorticosteroids, and about 60% will have 2 or more adverse events. Compared with age- and sex-matched controls, patients with giant cell arteritis have an increased risk for fractures and corticosteroid-related cataracts (9).

Adjunctive treatments are needed that would effectively reduce the dose and duration of glucocorticosteroid therapy and provide more durable remissions of giant cell arteritis. Other investigators have evaluated the utility of cytotoxic and anti-inflammatory agents in giant cell arteri-

tis. However, the reports have been anecdotal, of uncontrolled studies, or of controlled studies with conflicting results in terms of efficacy (11, 12).

Increased knowledge of cell types and mediators within vessels damaged by giant cell arteritis has led to speculation about the potential therapeutic role of several cytokine antagonists. Interleukin-1, interleukin-6, tumor necrosis factor (TNF)- α , and interferon- γ have been implicated in contributing to vascular injury in patients with giant cell arteritis (13-16). Published case studies reported

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Context

Up to 80% of patients with giant cell arteritis (GCA) experience complications related to glucocorticoid therapy. Case reports suggest that patients with GCA who received infliximab achieved sustained disease remission and independence from glucocorticoids.

Contribution

Patients with glucocorticoid-induced GCA remission were randomly assigned to infusions of infliximab, 5 mg/kg, or placebo at 0, 2, and 6 weeks and every 8 weeks thereafter. The investigators found that infliximab did not reduce rates of relapse or any secondary end point.

Caution

The study was small and stopped early (after week 22 of the planned 54 weeks), so it could not definitively identify harms or small benefits.

Implication

Infliximab is unlikely to cause large reductions in rates of relapse of GCA.

—The Editors

that some patients with giant cell arteritis or polymyalgia rheumatica who received the anti-TNF- α agent infliximab had sustained remission and became glucocorticosteroid-independent (17, 18). However, the investigators cautioned that randomized, controlled studies were needed to validate these results.

We report the results of the first randomized, placebo-controlled, double-blind, multicenter trial of standardized treatment with glucocorticosteroids and adjunctive treatment with placebo or infliximab in patients with newly diagnosed giant cell arteritis.

METHODS**Design**

We designed a multicenter, randomized, double-blind, placebo-controlled study to determine whether infliximab added to a standardized program of glucocorticosteroid therapy (equivalent daily doses of prednisone or prednisolone) in patients with newly diagnosed giant cell arteritis would decrease the frequency of relapse, cumulative glucocorticosteroid requirement, and glucocorticosteroid-associated toxicity. The study protocol was approved by the institutional review boards or ethics committees of the individual study sites. The study was conducted according to the current regulations of the U.S. Food and Drug Administration, the International Conference on Harmonization guidelines, and the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in any protocol-specific procedures. An independent safety monitoring committee reviewed safety information during the trial. The first patient was

enrolled on 22 October 2003, and the last patient completed the study on 29 July 2005.

The primary objective was to obtain preliminary evidence on the safety and efficacy of infliximab therapy in patients with glucocorticoid-induced remission of newly diagnosed giant cell arteritis, as measured by the proportion of patients who were relapse-free through week 22 and the incidence of adverse events. The secondary objective was to further evaluate the preliminary evidence of the efficacy of infliximab therapy, as measured by the proportion of patients who remained relapse-free through week 54, time to first relapse, levels of biochemical markers of inflammation and disease activity, and cumulative dose of glucocorticosteroids.

Setting

The study was conducted at 22 sites in the United States, United Kingdom, Belgium, Italy, and Spain.

Participants

To be eligible for the study, patients must have had a diagnosis of giant cell arteritis within 4 weeks of enrollment, satisfied the American College of Rheumatology criteria for giant cell arteritis (19), had an erythrocyte sedimentation rate 40 mm or greater in the first hour at the time of diagnosis, and achieved clinical remission before randomization. For at least 1 week before randomization, patients were required to be receiving prednisone or prednisolone at a stable dosage of 40 to 60 mg/d, have a normal erythrocyte sedimentation rate (<40 mm in the first hour, as determined by using the Westergren method), and have no symptoms or signs of active giant cell arteritis.

Patients were excluded if they had received a diagnosis of giant cell arteritis or polymyalgia rheumatica more than 4 weeks before screening, did not respond to glucocorticosteroid therapy within 5 days of initiation of therapy, received intravenous glucocorticosteroid therapy with an equivalent dose of methylprednisolone (>1000 mg/d for >3 days), or received other forms of immunosuppressive therapy (such as methotrexate, azathioprine, or other cytotoxic agents) or any investigational or biological agents within the 3 months before screening. Patients with screening blood test results within the following ranges were also excluded: leukocyte count less than 3.5×10^9 cells/L, neutrophil count less than 1.5×10^9 cells/L, hemoglobin level less than 85 g/L, platelet count less than 100×10^9 cells/L, or hepatic aminotransferase or alkaline phosphatase levels greater than 3 times the upper limit of normal. We excluded patients with serious or chronic infections in the previous 3 months; opportunistic infections within the 6 months before screening; cancer within the 5 years before screening (with the exception of treated and cured squamous or basal cell carcinoma of the skin); a history of severe congestive heart failure or demyelinating disease; current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease; a

transplanted organ (with the exception of corneal transplantation done more than 3 months before screening); or evidence of active or previous tuberculosis.

Randomization and Intervention

Patients were randomly assigned in a 2:1 ratio to receive infliximab, 5 mg/kg, or placebo by using adaptive treatment allocation (20, 21) stratified by baseline glucocorticosteroid dosage (40 to 50 mg/d or 51 to 60 mg/d prednisone equivalent). Patients received infusions at weeks 0, 2, and 6 and every 8 weeks thereafter. Allocation to treatment group was performed by using a central randomization procedure through an interactive voice response system. Patients, investigators, and study personnel were blinded to treatment assignments during the study; the site pharmacists, who prepared study medication, were not blinded to this information.

Infliximab and placebo were supplied as sterile, white, lyophilized powders that were reconstituted with sterile water for injection. The reconstituted placebo solution contained the same excipients as the infliximab solution but did not contain infliximab.

Glucocorticosteroid dosages were tapered according to a predefined schedule (Table 1). Each week, the daily dose of prednisone or prednisolone was decreased by 10 mg until the dosage reached 20 mg/d. It was then tapered by 2.5 mg until it reached 10 mg/d and then by 1 mg until the dosage was 0 mg/d. In the absence of a relapse, this schedule results in a glucocorticosteroid dosage of 10 mg/d after 4 months and no glucocorticosteroid use after 6 months. If a relapse occurred, the patient was to resume treatment with the previous higher dose of prednisone or prednisolone that provided disease remission, plus 10 mg/d. If the relapse resolved within 72 hours, the patient was to continue receiving that dosage for 2 weeks and then resume tapering according to the protocol. If relapse did not resolve within 72 hours, the patient was to receive another increase of 10 mg and resume treatment according to the protocol.

If relapse included visual symptoms, the patient was to receive at least 40 mg/d or the previous higher dosage of prednisone or prednisolone, plus 10 mg (whichever was higher). If the visual symptoms improved within 48 hours, the patient was to resume tapering according to the protocol above. If the visual symptoms did not resolve within 48 hours, the patient’s vision was threatened, or there was concern about any other catastrophic event, the investigator was to take any measures necessary according to clinical judgment to treat the patient, including but not limited to increasing the glucocorticosteroid dosage to more than 60 mg/d. If a patient received more than 60 mg of oral prednisone or prednisolone daily or more than 1000 mg of intravenous glucocorticosteroid daily for more than 3 days, study infusions were discontinued, but the patient continued to return for study visits.

Table 1. Schedule of Dosage Tapering for Glucocorticosteroid Therapy*

Week	Starting Glucocorticosteroid Dosage, mg/d		
	40	41–50	51–60
0	40	41–50	51–60
1	40	41–50	51–60
2	30	40	50
3	20	30	40
4	20	20	30
5	17.5	20	20
6	17.5	17.5	20
7	15	17.5	17.5
8	15	15	17.5
9	12.5	15	15
10	12.5	12.5	15
11	10	12.5	12.5
12	9	10	12.5
13	8	9	10
14	7	8	9
15	6	7	8
16	5	6	7
17	4	5	6
18	3	4	5
19	2	3	4
20	1	2	3
21	0	1	2
22		0	1
23	–	–	0
24	Discontinued before week 24		

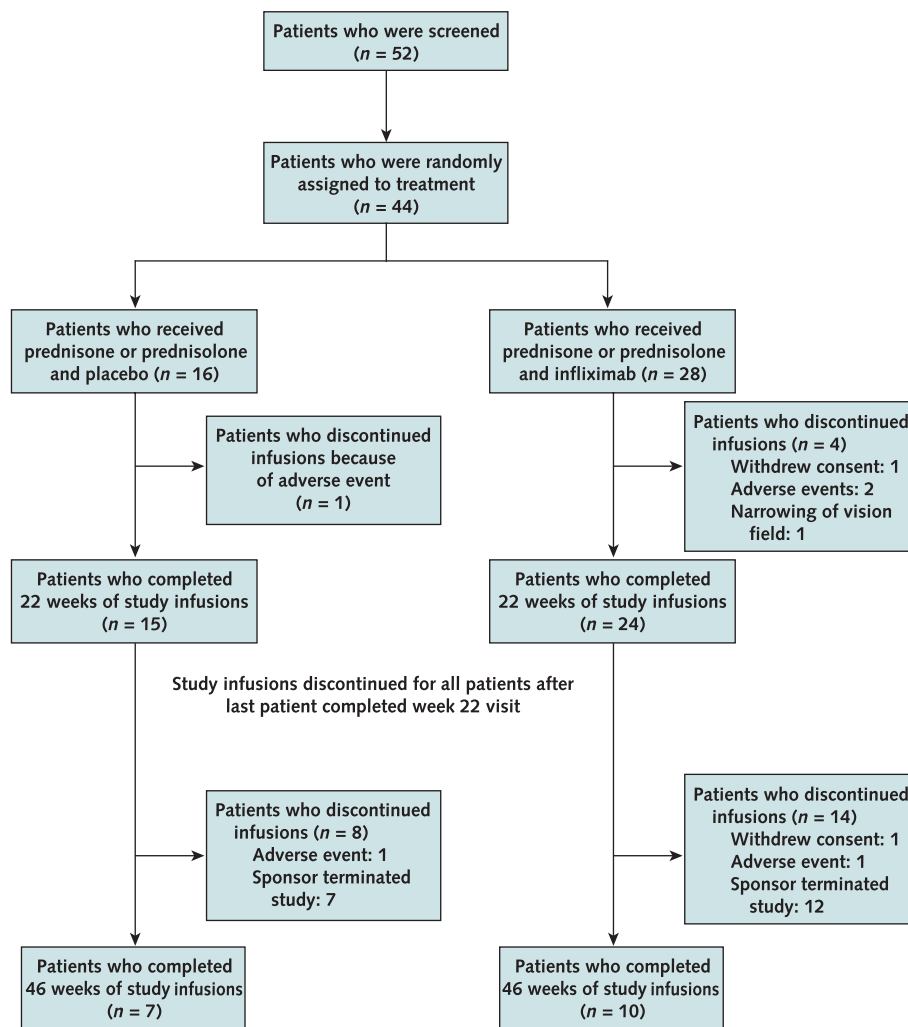
* Prednisone or prednisolone.

Outcomes and Measurements

Disease relapse was defined as an increase in erythrocyte sedimentation rate from normal to 40 mm or greater in the first hour, plus at least 1 symptom or sign of giant cell arteritis: sustained fever (temperature > 100.4 °F [38 °C] for > 1 week) that was not attributable to a cause other than giant cell arteritis; new or recurrent headache or pain or tenderness of the scalp; new, recurrent, or worsening ischemic retinopathy, optic neuropathy, or visual loss not attributable to other causes; new or recurrent pain or claudication of the tongue or jaw; new or recurrent claudication of the extremities; new, recurrent, or worsening thickness, tenderness, or ulcers or nodules over the temporal or occipital arteries; new, recurrent, or worsening angiographic abnormalities compatible with vasculitis of the aorta or its primary branches; new, recurrent, or worsening transient cerebral ischemia or stroke not attributable to cardiac arrhythmias or atherosclerotic disease; or new, recurrent, or worsening classic polymyalgia rheumatica-like symptoms, including malaise and fatigue that were unexplained by processes other than giant cell arteritis. In addition, patients with symptoms or signs of giant cell arteritis other than those listed above that could not be attributed to any cause other than giant cell arteritis and that were accompanied by an increase in the dose of glucocorticosteroids used to treat giant cell arteritis were considered to have had relapse.

Clinical remission was defined as an erythrocyte sedi-

Figure 1. Study flow diagram.



mentation rate less than 40 mm in the first hour and lack of the symptoms or signs of giant cell arteritis. Complete clinical remission was defined as maintenance of clinical remission for 12 weeks after discontinuation of glucocorticosteroid therapy. C-reactive protein was evaluated by using the Tinaquant assay (Roche, Indianapolis, Indiana) (normal range, 0 to 6 mg/L). Interleukin-6 was evaluated by using assays from R&D Systems (Minneapolis, Minnesota) (normal range, 0.45 to 9.96 ng/mL). All laboratory tests were done in a single batch by a central laboratory. Antibodies to infliximab, antinuclear antibodies, and antibodies to double-stranded DNA were evaluated at baseline, week 22, and 20 weeks after the last dose of study medication, by using a method described elsewhere (22). Antibodies to infliximab were assessed by measuring the optical density of antibodies in serum samples, using a double-antigen enzyme immunoassay in which infliximab served as the detection and capture reagent (23). Because the presence of infliximab in serum samples can interfere with de-

tection of antibodies to infliximab, samples were classified as inconclusive when infliximab levels in patient sera were greater than 0.1 $\mu\text{g/mL}$.

At each site, one clinician-investigator provided comprehensive care for an individual patient. A second independent physician-assessor (who did not have access to any other clinical information on the patient) evaluated the patient at each study visit and indicated on standardized forms whether symptoms or signs of giant cell arteritis were present or absent. Both physicians were blinded to treatment group assignment. Patients who discontinued study infusions were to be followed, according to the study schedule, for clinical and safety assessments.

Statistical Analysis

Primary study end points were the proportion of patients who remained relapse-free through week 22 and the incidence of adverse events. Secondary end points included the proportion of patients who remained relapse-free

through week 54, time to first relapse, levels of biochemical markers of inflammation and disease activity (erythrocyte sedimentation rate, C-reactive protein level, and interleukin-6 level), cumulative dose of glucocorticosteroid, the proportion of patients who remained relapse-free during tapering of the glucocorticosteroid dosage to 10 mg/d, and the duration of complete clinical remissions beyond week 22.

The Cochran–Mantel–Haenszel 2-sided chi-square test at a 5% level of significance with stratification by baseline prednisone or prednisolone dosage (40 to 50 mg/d or 51 to 60 mg/d) was used for the efficacy analysis. An intention-to-treat analysis was performed. Patients who discontinued treatment before week 22 because of lack of efficacy were considered to have had relapse. Patients who did not return for an evaluation or for whom data were insufficient to assess whether they were relapse-free before week 18 were considered to have had relapse. Patients who were relapse-free through evaluations at week 18 but who did not have sufficient evaluations at week 22 were considered to have achieved the primary end point (the week 18 value was carried forward). Patients whose glucocorticosteroid dose was increased to treat giant cell arteritis were considered to have had relapse because they did not follow

the glucocorticosteroid dose-tapering schedule; this was called an “analytical relapse.” A Kaplan–Meier analysis was used to estimate the proportion of patients who remained relapse-free through week 22.

The study was designed with a planned sample size of 42 patients (14 in the placebo group and 28 in the infliximab group). The power calculations were based on a chi-square test with no stratification and a type I error rate of 5%. The power of the study was expected to be greater than 80% if the relapse-free response rate was approximately 80% in the infliximab group and approximately 30% in the placebo group (11, 12).

A prespecified interim safety and efficacy analysis was performed by 1 of the authors after the last enrolled patient completed the week 22 study visit. The objective of the interim analysis was to aid in directing the clinical development program. The primary and major secondary end points were examined, although the specific end points to be examined were not prespecified. No formal stopping rules were prespecified for the interim analysis because the results were not expected to affect the conduct of the study. The independent safety monitoring committee was not involved in the interim analysis.

Table 2. Demographic and Clinical Characteristics of Patients at Randomization*

Characteristic	Placebo Group (n = 16)	Infliximab Group (n = 28)
Women, n (%)	11 (69)	24 (86)
White persons, n (%)	16 (100)	28 (100)
Median age (IQR), y	69.5 (65.0–77.0)	71.5 (66.0–75.5)
Median body weight (IQR), kg	67.8 (59.6–72.1)	66.9 (57.3–73.6)
Symptoms and signs of relapse of giant cell arteritis, n (%)		
Fever	8 (50)	5 (18)
Headache, or pain or tenderness of the scalp or temporal artery	14 (88)	21 (75)
Visual impairment	5 (31)	2 (7)
Pain or claudication of the tongue or jaw	7 (44)	12 (43)
Polymyalgia rheumatica–like symptoms	6 (38)	8 (29)
Extremity claudication	0 (0)	2 (7)
Angiographic abnormalities	1 (7)	1 (4)
Transient cerebral ischemia or stroke	1 (6)	0 (0)
Positive temporal artery biopsy	10 (67)†	24 (92)‡
Median serum creatinine concentration (IQR)		
μmol/L	79.5 (61.9–88.4)	70.7 (61.9–79.5)
mg/dL	0.9 (0.7–1.0)	0.8 (0.7–0.9)
Median hematocrit (IQR)		
0.38 (0.35–0.41)		0.39 (0.37–0.41)
Median erythrocyte sedimentation rate (IQR), mm/h		
At diagnosis of giant cell arteritis	76.0 (51.0–130.0)	79.0 (52.0–102.0)
At screening	41.5 (26.5–74.5)	49.5 (27.0–67.0)
At remission (week 0)	30 (22.0–44.5)	36 (18.0–50.0)
Median C-reactive protein level (IQR), mg/L§		
At screening	5 (4–18)	4 (4–10)
At remission (week 0)	6 (4–17)	5 (4–8)
Median interleukin-6 level (IQR), ng/L		
At screening	3.0 (1.3–11.8)	3.8 (1.6–5.0)
At remission (week 0)	4.1 (1.6–7.3)	3.2 (2.1–7.4)
Starting glucocorticosteroid dosage, n (%)		
40–50 mg/d	9 (56)	17 (61)
51–60 mg/d	7 (44)	11 (39)

* Values are those obtained at screening, unless otherwise specified. IQR = interquartile range.

† Percentage is based on 10 of 15 patients.

‡ Percentage is based on 24 of 26 patients.

§ Normal range, 0.0 to 0.6 mg/dL.

|| Normal range, 0.45 to 9.96 ng/L.

Table 3. Efficacy Outcomes at 22 Weeks

Outcome	Placebo Group (n = 16)	Infliximab Group (n = 28)
Patients who remained relapse-free*		
Total, n (%)	8 (50)	12 (43)
Difference (95% CI), percentage points		-7 (-38 to 23)
P value		0.65†
Patients whose glucocorticosteroid dosage was tapered to 10 mg/d		
Total, n (%)	12 (75)	17 (61)
Difference (95% CI), percentage points		-14 (-42 to 14)
P value		0.31†
Cumulative glucocorticosteroid dose at week 22		
Mean (SD), mg	3049.56 (769.54)	3154.10 (968.50)
Median (interquartile range), mg	2909.3 (2502.5–3143.0)	2982.0 (2461.0–3630.0)
P value		0.95‡
Glucocorticosteroid dosage at first relapse		
Mean (SD), mg/d	11.8 (16.9)	13.4 (17.5)
Median (interquartile range), mg/d	6.5 (0.5–17.5)	10 (1.0–20.0)
P value		0.59‡
Signs and symptoms of relapse through week 22, n (%)§		
Sustained fever	0 (0)	0 (0)
New or recurrent headache or pain or tenderness of the scalp or temporal artery	7 (44)	8 (29)
New, recurrent, or worsening visual symptoms specific to giant cell arteritis	1 (6)	6 (21)
New or recurrent pain or claudication of the tongue or jaw	3 (19)	4 (14)
New or recurrent claudication other than of the tongue or jaw	1 (6)	2 (7)
New, recurrent, or worsening temporal artery signs and symptoms	3 (19)	4 (14)
New, recurrent, or worsening angiographic abnormalities	0 (0)	0 (0)
New, recurrent, or worsening transient cerebral ischemia	0 (0)	1 (4)
New, recurrent, or worsening classic polymyalgia rheumatica-like symptoms	3 (19)	4 (14)
Other symptoms specified by the individual assessor	1 (6.3)	5 (18)
Other related symptoms specified by the investigator	1 (6.3)	3 (10.7)

* One patient in the infliximab group who withdrew consent at week 14 and did not return for the week 22 visit was considered to have had relapse.

† Cochran–Mantel–Haenszel 2-sided chi-square test stratified by baseline glucocorticosteroid dosage (40 to 50 mg/d or 51 to 60 mg/d).

‡ Analysis of variance on the van der Waerden normal scores.

§ Statistical testing was not done for this post hoc analysis because of the small number of patients and the error rates of statistical inferences caused by multiple comparisons.

All statistical analyses were done by using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

This study was funded by Centocor Research and Development, Inc. The study was led by a steering committee (Drs. Hoffman, Cid, Rendt-Zagar, Weyand, Stone, and Rahman), which was primarily responsible for the design of the study, interpretation of the results, and preparation of the manuscript. Dr. Xu (Centocor Research and Development, Inc.) conducted the statistical analysis. Employees of Centocor Research and Development, Inc., were also involved in the design of the study, interpretation of the results, and preparation of the manuscript. Dr. Hoffman wrote the first draft of the manuscript. All authors reviewed, contributed revisions to, and approved the manuscript before submission.

RESULTS

Patient Characteristics

Forty-four patients were enrolled, 16 in the placebo group and 28 in the infliximab group (Figure 1). Thirty-four patients (83%) had findings on baseline temporal artery biopsy that were consistent with giant cell arteritis. Baseline demographic and disease characteristics of the

treatment groups were similar, except that fever was more frequent in the placebo group than the infliximab group (50% vs. 18%; $P = 0.040$, 2-sided Fisher exact test) (Table 2). The difference between the placebo and infliximab groups in the frequency of temporal artery biopsies demonstrating giant cell arteritis was not statistically significant (67% vs. 92%; $P = 0.079$, 2-sided Fisher exact test).

Five patients discontinued treatment before the week 22 visit (4 in the infliximab group and 1 in the placebo group) (Figure 1). Four of these patients returned for the assessment visit at week 22; 1 patient in the infliximab group withdrew consent at week 14 and did not return for assessment.

Efficacy

The proportion of patients who were relapse-free through week 22 was similar between the placebo and infliximab groups (50% vs. 43%, respectively; $P = 0.65$) (Table 3). The groups did not differ in time to first relapse (Figure 2) or in interleukin-6 and C-reactive protein levels and erythrocyte sedimentation rates at first relapse (Figure 3).

Of the 24 patients who had relapse by week 22, 16 met the primary definition of relapse (an increase in the erythrocyte sedimentation rate ≥ 40 mm in the first hour and at least 1 of the signs or symptoms of giant cell arteritis

listed in the Methods section). Eight patients (4 placebo recipients and 4 infliximab recipients) had an analytical relapse, in that they did not meet the primary definition of relapse but their glucocorticosteroid dose was increased to treat giant cell arteritis. Of these 8 patients, 5 had signs and symptoms of giant cell arteritis but did not meet the erythrocyte sedimentation rate criterion in the primary definition, 2 met the erythrocyte sedimentation rate criterion but did not have a sign or symptom of giant cell arteritis, and 1 had neither a sign nor symptom nor met the erythrocyte sedimentation rate criterion. If patients with analytical relapse were considered to be relapse-free and only patients who met the primary definition were considered to have relapsed, 12 of 16 patients (75%) in the placebo group and 16 of 28 patients (57%) in the infliximab group would have been relapse-free through week 22.

The groups did not differ in the cumulative dose of prednisone or prednisolone at week 22 or the mean glucocorticosteroid dose at relapse (Table 3). Only 3 patients (25%) in the placebo group and 4 patients (17%) in the infliximab group were not receiving glucocorticosteroids at the time of relapse ($P = 0.34$).

The week 22 results were analyzed during the pre-planned interim analysis. The study steering committee and sponsor reviewed the results of the interim analysis and determined that although infliximab was generally well tolerated and had no unexpected safety issues, it appeared to provide no therapeutic benefit. Therefore, the steering committee and the sponsor decided to discontinue study infusions for all patients. Each patient had a safety follow-up visit 4 weeks after infusions were stopped. Patients also had a visit 20 weeks after their last dose of infliximab to evaluate antibodies to infliximab and disease activity. One patient in the infliximab group withdrew consent at week 26; all other patients who completed the week 22 visit returned for all follow-up visits.

Figure 2 shows the time to first relapse. The results after week 22 should be interpreted with caution because some patients completed the 54-week study, whereas only limited data were available for others because the study was terminated prematurely.

The mean number of relapses per patient during the study was 1.7 (SD, 1.45) in the placebo group and 1.8 (SD, 1.66) in the infliximab group. In the placebo group, 4 patients (25%) had no relapse, 5 patients (31%) had 1 relapse, 1 patient (6%) had 2 relapses, and 6 patients had 3 or more relapses (38%). In the infliximab group, 5 patients (18%) had no relapse, 10 patients (36%) had 1 relapse, 8 patients (29%) had 2 relapses, and 5 patients (18%) had 3 or more relapses ($P = 0.23$). Table 3 summarizes signs and symptoms of relapse.

Seven patients (44%) in the placebo group and 11 patients (39%) in the infliximab group achieved complete clinical remission (no sign of active giant cell arteritis for at least 12 weeks after discontinuation of prednisone or prednisolone therapy) ($P = 1.00$). The median duration of

complete clinical remission was 20.3 weeks (interquartile range, 18.0 to 25.0 weeks) in the placebo group and 21.0 weeks (interquartile range, 18.6 to 32.3 weeks) in the infliximab group. Of the patients who achieved complete clinical remission, 6 (86%) in the placebo group and 8 (73%) in the infliximab group later had relapse.

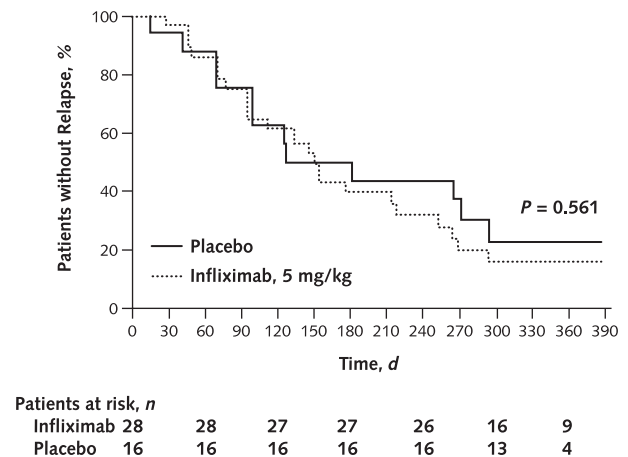
Pharmacokinetics

The median trough serum infliximab concentration in the infliximab group at week 22 was 1.7 $\mu\text{g/mL}$ (interquartile range, 0.0 to 5.1 $\mu\text{g/mL}$; range, 0.0 to 113.6 $\mu\text{g/mL}$).

Adverse Events

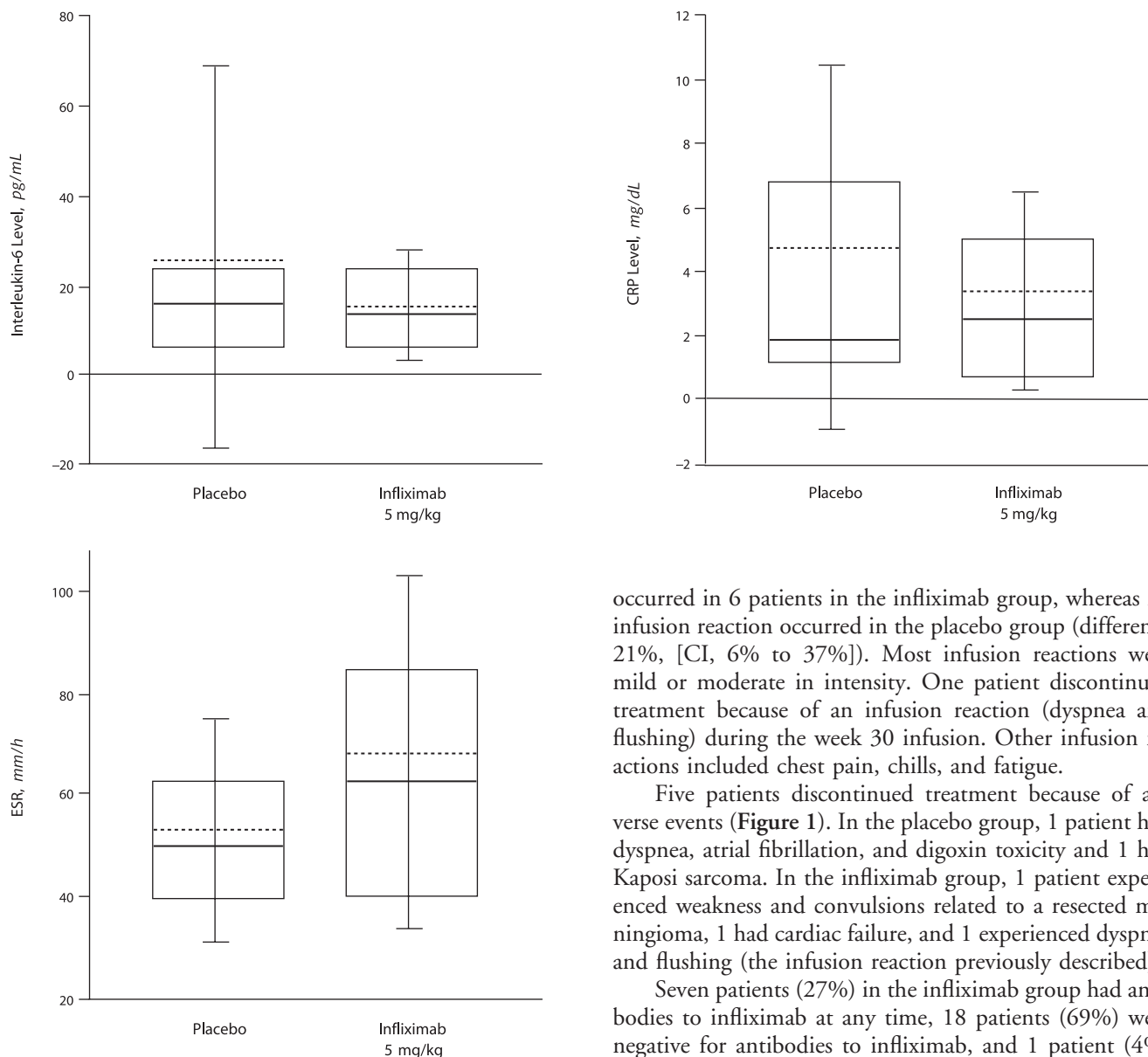
Patients in each group received an average of 7 study infusions, and the median total dose of infliximab was 35.0 mg/kg. The groups did not differ clinically or statistically in the frequency of adverse events or serious adverse events (Table 4). Although the incidence of infections was numerically higher among infliximab recipients than placebo recipients, the difference was not statistically significant (71% vs. 56%; difference, 15 percentage points [95% CI, -14 to 45 percentage points]). The incidence of infections requiring oral or parenteral antimicrobial treatment for each treatment group did not differ (57% of infliximab recipients vs. 50% of placebo recipients; difference, 7 percentage points [CI, -23 to 38 percentage points]). Four patients reported serious infections (3 [11%] in the infliximab group vs. 1 [6%] in placebo group; difference, 5 percentage points [CI, -12 to 21 percentage points]). The patient in the placebo group had ischemic colitis 13 days after the week 22 infusion. In the infliximab group, 1 patient had herpes keratitis in the right eye 35 days after the week 30 infusion, 1 had bronchitis 7 days after the week 2 infusion, and 1 had a *Staphylococcus aureus*-infected hema-

Figure 2. Kaplan–Meier estimate of the proportion of patients who remained relapse-free through the end of the study.



The groups did not differ significantly in the time to first relapse, according to a log-rank test.

Figure 3. Box plots showing interleukin-6 level, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) at the time of first relapse.



Solid horizontal lines represent medians, boxes represent interquartile ranges, dashed horizontal lines represent means, and error bars represent SDs. Values were available for 13 placebo recipients and 21 infliximab recipients.

toma 23 days after the week 2 infusion and pleuropneumonia 89 days after the week 46 infusion. There were no cases of tuberculosis or sepsis. One patient in the placebo group developed Kaposi sarcoma. No cases of cancer were observed in patients receiving infliximab.

An infusion reaction was predefined as any adverse event that occurred during an infusion or within 1 hour after completion of an infusion. Ten infusion reactions

occurred in 6 patients in the infliximab group, whereas no infusion reaction occurred in the placebo group (difference 21%, [CI, 6% to 37%]). Most infusion reactions were mild or moderate in intensity. One patient discontinued treatment because of an infusion reaction (dyspnea and flushing) during the week 30 infusion. Other infusion reactions included chest pain, chills, and fatigue.

Five patients discontinued treatment because of adverse events (Figure 1). In the placebo group, 1 patient had dyspnea, atrial fibrillation, and digoxin toxicity and 1 had Kaposi sarcoma. In the infliximab group, 1 patient experienced weakness and convulsions related to a resected meningioma, 1 had cardiac failure, and 1 experienced dyspnea and flushing (the infusion reaction previously described).

Seven patients (27%) in the infliximab group had antibodies to infliximab at any time, 18 patients (69%) were negative for antibodies to infliximab, and 1 patient (4%) had an inconclusive antibody status 20 weeks after the last dose of infliximab. Five patients (33%) in the placebo group and 13 patients (52%) in the infliximab group developed antinuclear antibodies during the study. Antibodies to double-stranded DNA were not found in the placebo group and developed in 16% of patients in the infliximab group. However, no clinical syndromes associated with antinuclear antibodies or antibodies to double-stranded DNA were observed.

DISCUSSION

To address the unmet need for a treatment that would allow patients with giant cell arteritis to reduce their dependence on glucocorticosteroids, we conducted the first

Table 4. Rates of Adverse Events and Development of Autoantibodies

Event	Placebo Group (n = 16)	Infliximab Group (n = 28)
Patients with adverse events, n (%)		
≥1 adverse event	15 (94)	26 (93)
≥1 serious adverse event	4 (25)	8 (29)
Discontinuation due to an adverse event	2 (13)	3 (11)
Infection		
All infections, n	23	47
Patients with ≥1 infection, n (%)	9 (56)	20 (71)
Patients with ≥1 infection requiring oral or parenteral antimicrobial treatment, n (%)	8 (50)	16 (57)
Patients with ≥1 serious infections, n (%)	1 (6)	3 (11)
Infusion reactions*		
Infusions, n	110	182
Infusion reactions, n	0 (0)	10 (5)
Patients with ≥1 infusion reactions, n (%)	0 (0)	6 (21)
Development of autoantibodies, n (%)		
Antinuclear antibodies (newly positive)	5 (33)	13 (52)
Antibodies to double-stranded DNA (newly positive)	0 (0)	4 (16)

* Defined as any adverse event reported during the infusion or within 1 hour after the infusion.

double-blind, randomized, placebo-controlled trial in which a biological agent was used as an adjunct to glucocorticosteroid therapy for giant cell arteritis. Our results failed to demonstrate that infliximab improved the duration of remissions or decreased the glucocorticosteroid requirement in patients with newly diagnosed giant cell arteritis. These conclusions were based on a duration of follow-up of at least 22 weeks for all patients and a median of 7 infliximab infusions per patient. The results are consistent with a difference in the proportion of relapse-free patients ranging from a 38% advantage for placebo to a 23% advantage for infliximab. The results are also consistent with a difference in the proportion of relapse-free patients whose glucocorticosteroid dosages were tapered to 10 mg/d, ranging from a 42% advantage for placebo to a 14% advantage for infliximab. Thus, our study provides evidence that infliximab therapy is unlikely to greatly reduce the proportion of patients with relapse of giant cell arteritis.

The study was not powered to detect modest effects of adding infliximab to glucocorticosteroid therapy for newly diagnosed giant cell arteritis. However, the expense and risk of the intervention would not likely be justified in routine practice if studies in a much larger sample demonstrated only a small benefit of infliximab.

Several matters regarding the study drug and trial design merit discussion. One might question whether a higher dose of infliximab might be efficacious for giant cell arteritis. The infliximab dose of 5 mg/kg, rather than the usual initial dose of 3 mg/kg used to treat for inflammatory arthritis, was chosen to reduce the possibility of failure merely because of an inadequate dose. The 5-mg/kg induction and maintenance regimen has been shown to be effective and well tolerated in patients with psoriasis (24), spon-

dyloarthropathy (25), and Crohn disease (26). Infliximab was not administered with concomitant methotrexate in these studies. We did not address whether efficacy may have been achieved by using even higher doses of infliximab, greater frequency of administration, or concurrent administration of methotrexate.

We found that approximately one quarter of patients who received infliximab developed antibodies to infliximab 20 weeks after the last dose was administered. Thus, for most patients, the lack of efficacy could not be attributed to antibodies to infliximab. In EXPRESS (European Infliximab for Psoriasis [Remicade] Efficacy and Safety Study), which studied infliximab therapy in patients with psoriasis (24), the rate of antibody formation to infliximab (27%) 20 weeks after the last dose was similar to that in our study. However, contrary to our results, the EXPRESS investigators found that infliximab was much more effective than placebo at reducing the signs and symptoms of psoriasis.

Salvarani and colleagues' study of polymyalgia rheumatica (27), a forme fruste of giant cell arteritis, further supports our findings. The researchers used a trial design that was similar to that of our study and found no statistically significant therapeutic benefit of infliximab. Thus, these 2 studies indicate that the addition of infliximab to glucocorticosteroids does not markedly decrease relapse rates or cumulative glucocorticosteroid requirements of patients with newly diagnosed giant cell arteritis or polymyalgia rheumatica. However, the role of anti-TNF-α therapy in patients with glucocorticosteroid-refractory giant cell arteritis or polymyalgia rheumatica has not been systematically studied.

Although TNF is found in abundance in biopsy samples with vascular damage from giant cell arteritis, the exact role of TNF in the pathogenesis of giant cell arteritis remains to be elucidated. It is possible that other pathways and mediators play more important or pivotal roles in the pathogenesis of giant cell arteritis.

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